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Abstract: Complex I (NADH dehydrogenase) and complex IV (cytochrome-c-oxidase) of the mitochondrial electron transport chain are reported to be affected by drugs used to treat psychiatric or neurodegenerative diseases, including antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia and antiparkinsonian drugs.
We conducted meta-analyses examining the effects of each drug category on complex I and IV. The electronic databases Pubmed, EMBASE, CENTRAL and Google Scholar were searched for studies published between 1970 and 2018. Of 3105 screened studies, 68 articles covering 53 drugs were included in the meta-analyses. All studies assessed complex I and IV in rodent brain at the level of enzyme activity.
Meta-analyses revealed that selected antidepressants increase or decrease complex I and IV, antipsychotics and stimulants primarily decrease complex I but increase complex IV, whereas anxiolytics, mood stabilizers, antidementia and antiparkinsonian drugs preserve or even enhance both complex I and IV. To determine potential contributors to the drug effects, we meta-analyzed the drugs' neurotransmitter receptor profiles and found that affinity to adrenergic (□1B), dopaminergic (D1/2), glutaminergic (NMDA1,3), histaminergic (H1), muscarinic (M1,3), opioid (OP1-3), serotonergic (5-HT2A, 5-HT2C, 5-HT3A) and sigma (□1) receptors contributed most to the effects. We discuss the drug effects in relation to pharmacological mechanisms of action that might have relevance for clinical and research applications.

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Multivariate meta-analyses of antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia and antiparkinsonian drug effects on mitochondrial complex I and IV in rodent models

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Summary

We conducted meta-analyses examining the effects of antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia and antiparkinsonian drugs on mitochondrial complex I and IV. The electronic databases Pubmed, EMBASE, CENTRAL, and Google Scholar were searched for studies published between 1970 and 2018. Results showed that antidepressants increase or decrease complex I and IV, antipsychotics and stimulants primarily decrease complex I but increase complex IV, whereas anxiolytics, mood stabilizers, antidementia, and antiparkinsonian drugs preserve or even enhance both complex I and IV. These effects could be related to the drugs' neurotransmitter receptor profiles. We discuss the drug effects in relation to pharmacological mechanisms of action that might have relevance for clinical and research applications.

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Abstract

Background: Complex I (NADH dehydrogenase) and complex IV (cytochrome-c-oxidase) of the mitochondrial electron transport chain are reported to be affected by drugs used to treat psychiatric or neurodegenerative diseases, including antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia, and antiparkinsonian drugs.

Methods: We conducted meta-analyses examining the effects of each drug category on complex I and IV. The electronic databases Pubmed, EMBASE, CENTRAL, and Google Scholar were searched for studies published between 1970 and 2018. Of 3105 screened studies, 68 articles covering 53 drugs were included in the meta-analyses. All studies assessed complex I and IV in rodent brain at the level of enzyme activity.

Outcomes: Meta-analyses revealed that selected antidepressants increase or decrease complex I and IV, antipsychotics and stimulants primarily decrease complex I but increase complex IV, whereas anxiolytics, mood stabilizers, antidementia, and antiparkinsonian drugs preserve or even enhance both complex I and IV. To determine potential contributors to the drug effects, we meta-analyzed the drugs' neurotransmitter receptor profiles and found that affinity to adrenergic (α1B), dopaminergic (D1/2), glutaminergic (NMDA1,3), histaminergic (H1), muscarinic (M1,3), opioid (OP1-3), serotonergic (5-HT_{2A}, 5-HT_{2C}, 5-HT_{3A}) and sigma (σ1) receptors contributed most to the effects.

Interpretation: We discuss the drug effects in relation to pharmacological mechanisms of action that might have relevance for clinical and research applications.

Funding: No specific funding.

Keywords: meta-analysis; psychotropic drugs; NADH dehydrogenase; cytochrome-c-oxidase.

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Research in context

Evidence before this study: Drugs used to treat psychiatric or neurodegenerative diseases, including antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia, and antiparkinsonian drugs are suggested to be one of the contributors to mitochondrial dysfunction observed in those disorders. Two enzymes have been shown to relate to mitochondrial function under those conditions, mitochondrial complex I (NADH dehydrogenase) and complex IV (cytochrome-c-oxidase). We aimed to meta-analyze the effects of each drug category on complex I and IV. We conducted a structured literature search in PubMed, EMBASE, CENTRAL, and Google Scholar to identify studies published between January 1970 and May 2018 using the search strings 'NADH dehydrogenase' OR 'cytochrome-c-oxidase' OR 'complex I' OR 'complex IV' AND 'antidepressants' OR 'antipsychotics' OR 'anxiolytics' OR 'mood stabilizers' OR 'stimulants' OR 'Alzheimer' OR 'Parkinson'. Aggregated data were collected containing qualitative information (i.e., drug names, drug mechanisms of action, and brain regions of interest (ROIs)), quantitative data (i.e., number of drug-administered and control animals, dosage, and duration of drug administration), and outcomes (effect sizes in terms of standardized mean differences (SMD) and p-values).

Added value of this study: This meta-analysis summarizes the findings of drugs used to treat psychiatric and neurodegenerative disorders with regard to their effects on mitochondrial complex I and IV and relates those findings to the drugs' neurotransmitter receptor profiles.

Implications of all the available evidence: Combined with existing evidence, the results of the meta-analysis may guide researchers and clinicals in the use of drugs to treat psychiatric and neurodegenerative disorders to consider how psychopharmacological agents and their neurotransmitter receptors profiles interact on mitochondrial function. Considering those relationships may help to reduce the burden of mitochondrial dysfunction in psychiatric and neurodegenerative conditions.

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Introduction

Impaired mitochondrial function is linked to the pathophysiology of major psychiatric disorders such as mood disorders and schizophrenia[1–4] and neurodegenerative disorders such as Alzheimer's and Parkinson's.[5] Mitochondrial function is essential for production of adenosine triphosphate (ATP), the main source of cellular energy. Impaired mitochondrial function results in decreased energy metabolism, reduced bioenergetics, oxidative stress, and apoptosis.[3]

Psychotropic medication used to treat psychiatric or neurodegenerative conditions may target mitochondrial dysfunction.[6–8] For instance, psychiatric drugs such as antidepressants are thought to inhibit mitochondrial respiration leading to decreased ATP production in animal models of depression.[9] Both typical and atypical antipsychotics impair mitochondrial function by inducing structural gene changes also implicated in depletion of ATP supply.[10] Anxiolytics such as benzodiazepines[7] and stimulants such as amphetamines[11] weaken mitochondrial function through the formation of free radicals, particularly reactive oxygen species. Conversely, mood stabilizers such as lithium or valproic acid have been shown to preserve or even enhance mitochondrial function by increasing the rate of cellular respiration.[10] Similarly, medication to treat neurodegenerative disorders, for example antidementia drugs such as cholinesterase inhibitors (ChEIs) or antiparkinsonian drugs such as the dopamine agonist levodopa[12] or monoamine oxidase inhibitors (MAOIs),[13] may have neuroprotective effects that restore and maintain mitochondrial function. Together, these effects may contribute to both adverse effects and efficacy of many psychotropic medications, not only in patients with mitochondrial disorders but also in the much wider population receiving these agents for psychiatric or neurodegenerative illnesses[14] as we have discussed in our previous meta-analysis.[15]

Prior to ATP generation, mitochondria direct electrons extracted from nutrients into a transmembrane proton gradient and this process is mediated by the electron transport chain (ETC). Two enzymes of the ETC located at the inner mitochondrial membrane are the most impaired in psychiatric and neurodegenerative disorders based on our recent meta-analysis[15] and the most affected ETC enzymes by psychotropic drugs.[16] The first enzyme, complex I (NADH dehydrogenase, NDU), is one of the entry enzymes of cellular respiration or oxidative phosphorylation in the mitochondrion. NDU is the largest multimeric ETC complex and a major contributor to the proton gradient across the

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mitochondrial inner membrane, which drives ATP production. The second enzyme of interest, complex IV (cytochrome-c-oxidase, COX), catalyzes the final step in the ETC. Due to its rate-limiting role in this oxidative process[17] and its coupling with neuronal activation,[18,19] COX is proposed as a key marker of mitochondrial as well as neuronal function.[20] The two enzymes interact in that an assembled complex IV is required to maintain the stability of complex I [21–23]. Both complex I and IV also represent clinically relevant targets due to their accessibility using novel *in-vivo* technologies assessing complex I redox states[24,25] or oxidized complex IV.[26]

We chose the seven drug categories of antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia, and antiparkinsonian drugs, not only because of their potential common effects on mitochondrial function, but also based on the overlapping indications for which they are used to treat in clinical practice. Antidepressants are used in mood and anxiety disorders, but are also frequently applied to treat depressive symptomatology in schizophrenia and both Alzheimer's and Parkinson's.[27,28] Antipsychotics are used in schizophrenia as well as mood disorders to ameliorate psychotic episodes and used as antidepressants and anti-manic treatment.[29] Mood stabilizers are typically used for recurrent mood disorders but atypical antipsychotics can also be beneficial in schizophrenia due to their anti-aggressive effects[30] and possible improvement of negative symptoms.[31] Anxiolytics and stimulants are commonly given alone or in combination with antidepressants to treat comorbid anxiety,[32] fatigue, or attention deficits.[33,34] Antidementia drugs are not only used in Alzheimer's to improve cognitive function but also in Parkinson's[35] and schizophrenia[36] to treat comorbid dementia symptoms.

Besides the overlap in clinical application, the seven drug categories also show similarities in their mechanisms of action and neurotransmitter receptor and transporter binding profiles. Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or norepinephrine and dopamine reuptake inhibitors (NDRIs), primarily increase the levels of the monoamine neurotransmitters serotonin (5-hydroxytryptamine, 5-HT), norepinephrine, and dopamine (D) by inhibiting their reuptake at the corresponding transporters (SERT, NET, DAT);[37–42] to a lesser extent, some antidepressants also interact with adrenergic (α,β), glutaminergic (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, AMPA, N-methyl-D-aspartate, NMDA), histaminergic

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(H), muscarinic (M), melatonergic (MT), and sigma (σ) receptors. Typical antipsychotics exert their clinical effects as D2 receptor antagonists as their common target[43,44] and 5-HT_{2A} receptor antagonists for atypical antipsychotics.[45] Occupancy of other 5-HT receptors and α, H, M receptors contributes to side effects and adverse effects.[46–48] Anxiolytics such as benzodiazepines exert their various effects through allosteric modulation of gamma-aminobutyric acid (GABA-A) receptor.[49] Stimulants work by releasing dopamine and also have a moderate affinity for monoamine transporters (SERT, NET, DAT)[50,51] and to a lesser extent α and D receptors.[52] Similarly, antidementia drugs such as cholinesterase inhibitors (ChEIs) and antiparkinsonian drugs such as the dopamine agonist levodopa target D receptors, inhibit acetylcholine (ACh) catabolism and have down-stream effects on 5-HT, α, DAT and NMDA receptors.[53] These and other receptors have been shown to affect mitochondrial activities and vice versa.[54,55]

Numerous excellent reviews[6,7,9–13] have discussed the detailed effects on complex I and IV caused by each of the above-mentioned drug categories. A meta-analysis summarizing the findings across these drugs cannot be found in the literature. We conducted a literature review, screening for suitable papers and then conducted a meta-analysis examining the effects of each drug category on complex I and IV. This work extends our previous meta-analysis focusing on psychiatric and neurodegenerative disease levels.[15]

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Materials and methods

Literature search and study identification

We conducted a structured literature search in PubMed, EMBASE, CENTRAL, and Google Scholar to identify studies published between January 1970 and May 2018 using the search strings 'NADH dehydrogenase' OR 'cytochrome-c-oxidase' OR 'complex I' OR 'complex IV' AND 'antidepressants' OR 'antipsychotics' OR 'anxiolytics' OR 'mood stabilizers' OR 'stimulants' OR 'Alzheimer' OR 'Parkinson'. We additionally manually reviewed reference lists in all retrieved articles for related publications. Inclusion criteria were: studies published in the English language, studies investigated complex I and/or complex IV, studies reporting data in rodent disease models in comparison with a control group. Exclusion criteria were: studies in human patient populations, studies in other tissues than brain tissue, cellular studies, genetic studies, case reports, and publications not reporting original data.

Data extraction

Aggregated data were extracted for each of the seven drugs categories: antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia, and antiparkinsonian drugs. Aggregated data contained qualitative information (i.e., drug names, drug mechanisms of action, and brain regions of interest (ROIs)), quantitative data (i.e., number of drug-administered and control animals, dosage, and duration of drug administration), and outcomes (effect sizes in terms of standardized mean differences (SMD) and p-values). In case of aggregated data not presented in the text, the authors were contacted for permission to reuse original data or data were read from figures. Mechanisms of action and receptor affinity profiles of each drugs were derived from DrugBank,[56] when available.

Multivariate random-effect meta-analyses

Three separate meta-analyses were computed for complex I and IV separately to estimate: 1) the effects of drugs; 2) the effects of mechanisms of action; and 3) the effects of receptor affinity.

Moderators were built for each meta-analysis. 'Drug' moderators were based on the International Nonproprietary Names (INN) of the corresponding active pharmaceutical ingredients (e.g.,

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‘escitalopram’ for cipralex). ‘Mechanism of action’ moderators were built by categorizing each drug according to its corresponding primary drug mechanism (e.g., ‘escitalopram’ was categorized as ‘SSRI’); drugs with unknown mechanisms of action were categorized according to their therapeutic uses (e.g., ‘valproic acid’ was categorized as ‘antiepileptic drug (AEG)’). ‘Receptor affinity’ moderators were built by assigning each drug to its corresponding affinity for one or more of the various neurotransmitter receptors, transporters, or enzymes,[56] if available. The type of receptor binding, i.e., agonism or antagonism (coded 1 and -1), was treated as a covariate. Not considered was binding affinity (i.e., the inhibitory constant, Ki), since it is not available for all drugs.

All meta-analyses were performed using a multivariate, random-effect model based on the Metafor package[57] as implemented in R.[58] The multivariate model accounted for heterogeneity and dependency in the underlying true effects of multiple moderators that could overlap within subjects and studies (random factors). To adjust for dosage (mg/day) and administration duration (days) of the specific drugs, categorical dummy covariates were used. To adjust for sample size, effects were weighted based on study size. To allow for heterogeneity differences between moderators, an unstructured variance-covariance matrix was applied (function rma.mv; observed effects = SMD + dosage + duration; variance-covariance matrix = COV; weight = study size; variance structure = UN; moderators = ‘drugs’ OR ‘mechanism of action’ OR ‘receptor affinity : type’; random factors = subject + study; method = REML). A Wald-type test[57] was used to compare subgroup estimates between complex I and IV.

Heterogeneity was assessed using Cochran's Q-test and the inconsistency I^2 statistic that directly indicates to what extent each outcome contributes to the total variance. Publication bias was assessed using Egger’s regression analysis.

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Results

Data extraction

Of 3105 screened studies, 68 studies were eligible for the meta-analyses (**Tab. 1, Dataset S1**) on antidepressants (AD), antipsychotics (AP), anxiolytics (AX), mood stabilizers (MS), stimulants (ST), antidementia drugs (ADD), and antiparkinsonian drugs (APD). In total, studies covered 53 drugs (AD N = 18, AP N = 10, AX N = 3, MS N = 5, ST N = 4, ADD N = 7, APD N = 7). The number of studies reporting on complex I (total N = 72, AD N = 24, AP N = 10, AX N = 4, MS N = 10, ST N = 9, ADD N = 6, APD N = 9) and complex IV (total N = 62, AD N = 26, AP N = 9, AX N = 3, MS N = 10, ST N = 6, ADD N = 5, APD N = 3) varied between drug categories, some of them reporting the same drug in more than one drug category. All studies analysed complex I and IV at the level of enzymatic activity in brain tissue from rodents (rats or mice) decapitated after drug administration. No eligible studies were found in healthy human brain tissue. Complex I and IV were analysed either in selected ROIs (AD N = 24, AP N = 7, AX N = 2, MS N = 9, ST N = 8, ADD N = 4, APD N = 7) and/or in brain homogenates (AD N = 14, AP N = 9, AX N = 2, MS N = 3, ST N = 5, ADD N = 4, APD N = 2). Drugs were investigated in one/two or more dosage steps (AD N = 18/10, AP N = 6/6, AX N = 3/1, MS N = 9/2, ST N = 5/4, ADD N = 4/2, APD N = 8/1). Mean (range) duration of drug administration was similar between drug categories (AD = 11 (1-28) days; AP = 17 (1-90) days; AX = 12 (1-30) days; MS = 14 (1-42) days; ST = 12 (1-28) days; ADD = 9 (1-21) days; APD = 5 (1-60) days). Mean number of animals per study (i.e., sum of drug-administered animals plus control animals) was also similar between drug categories (AD N = 14, AP N = 11, AX N = 21, MS N = 13, ST N = 13, ADD N = 15, APD N = 11). Control animals received saline or were sham groups in diseases models. Considering all above-mentioned factors, drug category, enzymes, selected ROIs, dosage, and administration duration, 1215 data points were extracted. Mechanisms of action and receptor affinity profiles collected based on previous work[56] are provided in **Tab. 1, Fig. S1, Dataset S2.**

Multivariate random-effect meta-analyses

Meta-analyses assessed complex I and IV enzyme activity regarding the 1) effects of drugs (**Fig. 1**), 2) effects of mechanisms of action (**Fig. 2**), and 3) effects of receptor affinity (**Fig. 3**).

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Drugs

Antidepressants had negative effects on complex I for desipramine ($p = 0{\cdot}026$) and escitalopram ($p < 0{\cdot}0001$), whereas positive effects were observed for agomelatine ($p = 0{\cdot}00017$), paroxetine ($p = 0{\cdot}034$), and sertraline ($p < 0{\cdot}0001$) consistent with decreased versus increased NDU enzyme activity. Negative effects on complex IV were found for amitriptyline ($p = 0{\cdot}023$), desipramine ($p < 0{\cdot}0001$), fluoxetine ($p = 0{\cdot}045$), fluvoxamine ($p < 0{\cdot}0001$) and mirtazapine ($p = 0{\cdot}046$), whereas positive effects were observed for ketamine ($p = 0{\cdot}00021$), nortriptyline ($p < 0{\cdot}0001$), trazodone ($p = 0{\cdot}0014$), and sertraline ($p = 0{\cdot}023$). Differences in drug effects between complex I and IV were observed for agomelatine ($p = 0{\cdot}0003$), escitalopram ($p < 0{\cdot}0001$), paroxetine ($p = 0{\cdot}048$), and sertraline ($p = 0{\cdot}023$) as assessed using a Wild-type test.

Antipsychotics that had negative effects on complex I included chlorpromazine ($p < 0{\cdot}0001$), thiothixene ($p = 0{\cdot}00012$), and haloperidol ($p < 0{\cdot}0001$) consistent with decreased NDU enzyme activity. By contrast, positive effects on complex IV were observed for haloperidol ($p = 0{\cdot}039$) and risperidone ($p = 0{\cdot}00023$) indicating increased COX enzyme activity. All drug effects were significantly different between complex I and IV (chlorpromazine $p < 0{\cdot}0001$, haloperidol $p < 0{\cdot}0001$, risperidone $p = 0{\cdot}023$, thiothixene $p = 0{\cdot}001$) as assessed using a Wild-type test.

Anxiolytics had a positive effect on complex IV for diazepam ($p = 0{\cdot}0014$), and no detectable effects were found on complex I.

Mood stabilizers had a positive effect on complex I for lithium ($p = 0{\cdot}02$) and on complex IV for gabapentin ($p = 0{\cdot}047$).

Stimulants having negative effects on complex I included amphetamine ($p = 0{\cdot}0099$), mazindol ($p < 0{\cdot}0001$), methamphetamine ($p = 0{\cdot}0012$), and methylphenidate ($p < 0{\cdot}0001$). There were no significant effects on complex IV.

Antidementia drugs having positive effects on complex IV included memantine ($p = 0{\cdot}034$) and latrepirdine ($p = 0{\cdot}029$). There were no significant effects on complex I.

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Antiparkinsonian drugs having a positive effects on both complex I and complex IV were limited to selegiline ($p = 0{\cdot}013$ and $p = 0{\cdot}0033$, respectively), without significant differences between complex I and IV effects.

Mechanisms of action

Categorizing drugs according to their mechanisms of action revealed only few relevant findings compared to the abovementioned analysis. Negative effects on complex I were observed for typical antipsychotics ($p < 0{\cdot}0001$; Wild-type test $p < 0{\cdot}0001$), whereas lithium ($p = 0{\cdot}018$) and NDDIs ($p = 0{\cdot}01$; Wild-type test $p = 0{\cdot}025$) had positive effects. Positive effects on complex IV were also found for both AEGs ($p = 0{\cdot}046$) and NMDA antagonists ($p = 0{\cdot}0024$) (**Fig. 2**).

Receptor affinity

Receptor affinity profiles were available for 45 drugs[56] (out of 56 drugs) (antidepressants N = 17 (out of 18 drugs), antipsychotics N = 10 (out of 10 drugs), anxiolytics N = 2 (out of 3 drugs), mood stabilizers N = 4 (out of 5 drugs), stimulants N = 4 (out of 4 drugs), antidementia drugs N = 4 (out of 7 drugs), antiparkinsonian drugs N = 4 (out of 7 drugs)) (**Fig. S1, Dataset S2**). The results shown in **Fig. 3** thus represent information derived from combinations of drugs that share high affinity for a specific receptor but may differ in their affinity for other receptors.

For complex I, negative effects were found for 5-HT_{2A} ($p = 0{\cdot}0044$), α1B ($p = 0{\cdot}027$), D1 ($p = 0{\cdot}00013$), D2 ($p = 0{\cdot}0021$), H1 ($p = 0{\cdot}022$), M1 ($p = 0{\cdot}017$), and M3 ($p = 0{\cdot}024$), whereas positive effects were observed for σ1 ($p < 0{\cdot}0001$). For complex IV, negative effects were found for 5-HT_{3A} ($p = 0{\cdot}035$), DAT ($p = 0{\cdot}0035$), and NET ($p = 0{\cdot}014$), whereas positive effects were observed for 5-HT_{2C} ($p = 0{\cdot}022$), NMDA1,3 ($p = 0{\cdot}00012$), OP1 ($p = 0{\cdot}0018$), OP2 ($p = 0{\cdot}0056$), OP3 ($p = 0{\cdot}016$), and σ1 ($p = 0{\cdot}021$). Differences in receptor effects on complex I and IV were found for 5-HT_{2A} ($p = 0{\cdot}003$), α1A ($p = 0{\cdot}021$), α1B ($p = 0{\cdot}021$), D1 ($p = 0{\cdot}0002$), D2 ($p = 0{\cdot}014$), H1 ($p = 0{\cdot}026$), M1 ($p = 0{\cdot}045$), NMDA1,3 ($p = 0{\cdot}003$), and σ1 ($p = 0{\cdot}009$) as assessed using a Wild-type test.

None of abovementioned meta-analyses revealed relevant interaction effects with selected ROIs and we therefore do not report the corresponding results.

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Heterogeneity and publication bias

Overall, there was a high degree of heterogeneity as indicated by significant Q-statistics ($p < 0{\cdot}05$) and large I^2 values (**Tab. 2**). Putative low heterogeneity was observed for stimulants in complex I ($Q = 45{\cdot}93$, $p = 0{\cdot}434$, $I^2 = 11\%$), anxiolytics in complex IV ($Q = 4{\cdot}57$, $p = 0{\cdot}102$, $I^2 = 82\%$), and antiparkinsonian drugs in complex IV ($Q = 5{\cdot}58$, $p = 0{\cdot}589$, $I^2 = 34\%$), perhaps explained by the small study numbers in those drug categories (**Tab. 1**). Publication bias as assessed using Egger's regression test (**Tab. 2**) revealed non-significant results for all drug categories indicating no relevant publication bias.

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Discussion

This meta-analysis finds many drugs used to treat psychiatric and neurodegenerative disorders to affect mitochondrial complex I and IV. Overall antidepressants show the most heterogenous effects on complex I and IV with some exhibiting negative effects while others have positive effects. Antipsychotics and stimulants primarily decrease complex I but increase complex IV. By contrast, anxiolytics, mood stabilizers, antidementia, and antiparkinsonian drugs affect both complex I and IV positively. To narrow down potential contributors to the drug effects, we meta-analysed mechanisms of action and receptor profiles and found that antagonism of adrenergic (α1B), dopaminergic (D1,2), histaminergic (H1), muscarinic (M1,3) and serotonergic (5-HT_{2A}) receptors result in negative effects on complex I, whereas agonism of sigma (σ1) receptors increases complex I. By contrast, antagonism of serotonergic (5-HT_{3A}) receptors as well as inhibition of DAT and NET are associated with decreases in complex IV, whereas antagonism of glutaminergic (NMDA1,3) and serotonergic (5-HT_{2C}) receptors as well as agonism of opioid (OP1-3) and sigma (σ1) receptors results in positive effects on complex IV. These findings support a relationship between drug effects and receptor affinity profiles and mitochondrial complex I and IV, which may have relevance for selection of treatment with low mitochondrial toxic potential in psychiatric and neurodegenerative conditions as we have discussed in our previous meta-analysis focusing on psychiatric and neurodegenerative disease levels.[15]

Antidepressants

Antidepressants have heterogenous effects on complex I and IV independent of their canonical mechanisms of action (**Fig. 1 & 2**). For example, while some SSRIs exhibit negative effects such as escitalopram on complex I[59] or fluoxetine and fluvoxamine on complex IV,[60–64] other SSRIs have positive effects such as paroxetine on complex I[65,66] and sertraline on both complex I and IV.[67,68] Similarly, some norepinephrine reuptake inhibitors (NRIs) such as desipramine and amitriptyline reveal strong negative effects on complex I and/or IV,[16,64,69] whereas nortriptyline, another NRI, affects complex IV positively.[66] Noradrenergic and specific serotonergic antidepressants (NaSSAs) such as mirtazapine have negative effects on complex IV (and I),[16] while serotonin antagonists and

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reuptake inhibitors (SARIs) such as trazodone were observed to have a positive effect on complex IV.[68] The heterogeneity of these effects is likely related to the broader receptor profile of antidepressants such as antagonizing or agonizing adrenergic, dopaminergic, histaminergic, muscarinic, opioid, serotonergic and sigma receptors and inhibiting DAT, NET and SERT transporters. The combination of those receptor profiles in different antidepressants may lead to opposite effects on complex I and IV (**Fig. 3**). For example, antagonism of most serotonergic, i.e., 5-HT_{1A}, 5- $HT_{2A/C}$, 5-HT_3, receptors has previously been shown to inhibit complex I, mitochondrial biogenesis and oxidative metabolism in rodent hippocampal neurons,[70] kidney,[71,72] and cardiac mitochondria,[73] respectively, in line with our findings (**Fig. 3**). Similarly, antagonism of muscarinic (M)[74] and histaminergic, especially H3 brain-specific receptors,[75] inhibits natural mitochondrial protection from apoptotic and oxidative stress, the latter potentially antagonizing neuroprotective NMDA receptor activation.[76] Likewise, antagonism of adrenergic α[77] and β[78,79] receptors can inhibit mitochondrial function by blocking their role in the stimulation of mitochondrial biogenesis (**Fig. 3**). By contrast, opioid receptors, especially delta-opioid receptors (OP1) (**Fig. 3**), are neuroprotective, particularly in cerebral cortex, by stabilizing ionic homeostasis, increasing antioxidant capacity and attenuating disrupted neuronal transmission.[80,81] Also, sigma (σ) receptor agonism, especially σ1 receptor (**Fig. 3**), which functions as a sensor for normal mitochondrial calcium (Ca^{2+}) operation[82] and σ1-ligands are thus discussed as protein-based pharmacological treatment to treat mitochondrial dysfunction in psychiatric and neurodegenerative conditions.[83]

Notably, agomelatine, a norepinephrine and dopamine disinhibitor (NDDI) and melatonergic MT1/2 agonist, was found to have a prominent positive effect on complex I in this meta-analysis (**Fig. 1 & 2**). Previous work showed that low-dose agomelatine increases complex I activity in prefrontal cortex, cerebellum, and striatum, while decreasing it in the posterior cortex, whereas high-dose agomelatine decreases complex I activity in all those brain regions.[84] Agomelatine is thought to protect against pathology-induced decreases in complex I[85–87] by decreasing pathologically enhanced intracellular Ca^{2+} levels[88] and inhibiting the opening of mitochondrial permeability transition pores.[89] This effect may be mediated by its agonist action at MT1 and MT2 receptors that have antioxidant activity and free radical scavenging, both actions are therapeutic for oxidative stress.[90]

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Ketamine, a NMDA receptor antagonist, used as rapidly acting antidepressant,[91] was found to have a positive effect on complex IV (and to some extent complex I)[92–95] (**Fig. 1 & 2**). Previous work showed that ketamine increases complex IV but not complex I activity.[93] In the short-term (1 hour after treatment) it has been shown to increase complex IV activity in striatum and hippocampus but not in prefrontal cortex, whereas more delayed responses (after 6 hours of treatment) were described only in striatum.[92] Ketamine also increases other enzymes such as peroxiredoxins that enhance cellular antioxidant capacity by combating reactive oxygen species, reducing protein damage and adjusting homeostatic redox, which supports the role of mitochondria as downstream effectors mediating its rapid antidepressant action.[96] Ketamine's effects on complex IV may be reflected in the strong positive effects of the ionotropic glutamatergic NMDA receptor (**Fig. 3**) that is co-regulated by the same transcription factors as COX[18,19] and thought to restore the neuroprotective glutamatergic system.[97]

Antipsychotics

Antipsychotics show strong negative effects on complex I primarily accounted for by the typical antipsychotics, chlorpromazine, thiothixene, and haloperidol[98–104] (**Fig. 1 & 2**). Antagonism of dopaminergic, primarily D2, receptors by typical antipsychotics (**Fig. 3**) may lead to dopamine accumulation in mitochondria resulting in D2-induced inhibition of complex I,[105,106] which in turn has been associated with the induction of extrapyramidal side effects (EPS).[101,107] By contrast, haloperidol affects complex IV positively[102] as supported by our analysis (**Fig. 1**). These opposing haloperidol effects on complex I and IV are thought to result from either up-stream (D2-induced) inhibition of complex I in the ETC[21–23] or reflect (D2-independent) enhanced functional neuronal activation due to the coupling between COX and neuronal activity.[19] This in turn may be clinically reflected in the delayed therapeutic effects of neuroleptic agents.[102]

By contrast, atypical antipsychotics were observed to have no significant effects besides an isolated increase in complex IV by risperidone[65,98,99] (**Fig. 1**), which might be related to their lower D2 receptor affinity for serotonergic 5-HT_{2A},[108] adrenergic, muscarinic, and histaminic receptors,[44,109] which also implies lower rates of EPS.

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Together, these results support a complex I participation in dopamine-induced mitochondrial dysfunction such as observed in postmortem brain samples from deceased schizophrenic patients,[110–115] whereas the reduction in COX activity observed in schizophrenia[15,116] is thought to be independent of antipsychotic treatment.[102]

Anxiolytics

Evidence that anxiolytics have weak positive effects on complex IV, is not certain because of the small number of studies in this drug category. Only the benzodiazepine, diazepam, a GABA-A receptor positive allosteric modulator (PAM) (**Fig. 2**), enhanced complex IV (**Fig. 1**), suggesting that this GABA-A effect may not be the mechanism because all the other benzodiazepines do not have this effect on complex IV. The possibility of an effect of GABA-A receptors (**Fig. 3**) was thus not supported by our analysis but needs to be further evaluated when more subjects have been studied because of the known neuroprotective effects of GABA-A agonists that may preserve COX activity by maintaining mitochondrial membrane potential, inhibiting downstream release of cytochrome c, and apoptotic signaling.[117,118]

Mood stabilizers

Mood stabilizers show positive effects on both complex I and IV. Lithium, the most established mood stabilizer, increases complex I[16,119–124] (**Fig. 1 & 2**) by acting on intracellular Ca^{2+} signaling, inhibiting inositol monophosphatase,[4] and modulating the neuroprotective ionotropic glutamatergic AMPA receptor,[125–128] which, however, did not reach significance in our analysis (**Fig. 3**). These findings are consistent with human studies in postmortem brain of patients with bipolar depression that report lithium stimulating mitochondrial complex I (but not complex IV) at clinically relevant concentrations.[129,130]

Antiepileptics, also used as mood stabilizers, such as gabapentin, enhance complex IV[131,132] (**Fig. 1 & 2**), which may be related to their NMDA receptors antagonism[133] since it showed positive effects for other drugs as well (**Fig. 3**). The main action of AEDs is to increase GABA transmission, which did show effects (**Fig. 3**). Although, little is known about the impact of AEDs on mitochondria, our findings suggest that some AEDs like gabapentin and lamotrigine) have beneficial effects despite

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interfering with ETC-related membrane potential, mitochondrial biogenesis, morphology, dynamics, and survival.[134]

Stimulants

Stimulants such as amphetamine, methamphetamine, mazindol and methylphenidate, all dopamine reuptake inhibitors (DRIs), affect complex I negatively[135–143] (**Fig. 1 & 2**) potentially related to their inhibition of DAT, NET and SERT transporters[144] (**Fig. 3**). Amphetamine enters and accumulates in mitochondria thereby dissipating the electrochemical gradient established by the ETC, inhibiting complex I and releasing cytochrome c, which in turn may induce the aforementioned interaction with complex IV and apoptosis.[145]

Antidementia drugs

Antidementia drugs have no effects on complex I and it is not clear whether they affect complex IV (**Fig. 1 & 2**). Cholinesterase inhibitors (ChEIs), the most established antidementia drugs, inhibit ACh catabolism leading to its accumulation, greater stimulation of nicotinic and muscarinic receptors, and disrupted neurotransmission that may explain some of their positive effects on learning, memory, and other cognitive functions in Alzheimer's.[146] Memantine, a NMDA antagonist, also has a positive effect on complex IV[147–149] (**Fig. 1 & 2**) reflected in the strong positive NMDA receptor effect (**Fig. 3**) that is thought to restore unbalanced homeostasis in the glutamatergic system.[150] Positive effects on complex IV were also observed for latrepirdine[149] (**Fig. 1**); however, since its mechanism of action is not fully known its receptor affinity profile could not be assessed in the present analysis,[56] but may include neuroprotective effects by blocking neurotoxic Alzheimer beta-amyloid via modulation of NMDA receptors.[151,152] Together, these findings suggest that the well-documented deficit in complex IV in Alzheimer's,[5,153,154] thought to be due to neuronal toxicity and hypometabolism induced by beta-amyloid accumulation in mitochondria[155–158] can be addressed with antidementia drugs.

Antiparkinsonian drugs

The most established antiparkinsonian drug, levodopa, an indirect dopamine agonist, was not found to affect complex I or IV.[159–163] This is in contrast to previous findings stating that levodopa significantly

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increases complex I activity, while not changing complex IV activity[161] or that levodopa does not alter complex I activity by itself, but attenuates the decrease in complex I activity induced by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), the prodrug to the neurotoxin MPP^+ (1-methyl-4-phenylpyridinium) which causes permanent symptoms of Parkinson's disease by destroying dopaminergic neurons in the substantia nigra.[159]

However, a weak positive effect on both complex I and IV was observed for selegiline, a selective irreversible MAO-B inhibitor in lower doses[164] (**Fig. 1 & 2**). Selegiline is thought to be neuroprotective by suppressing Ca^{2+} efflux through mitochondrial permeability transition pores thereby inducing anti-apoptotic, pro-survival genes, though this is disputed.[165] Selegiline could thus protect mitochondrial function when used to treat Parkinson's symptoms in combination with levodopa,[166] but also off-label as palliative treatment for Alzheimer's dementia[167] and, as part of its antidepressant effects in major depressive disorder.[168]

Methodological considerations

The present meta-analysis focused on rodent studies since no eligible studies were found in healthy human brain tissue. Doses and tissue levels of the cited drugs achieved in rodents are often much higher than those achieved in clinical treatment in humans. This is usually done to maximize effect but may create effects that are not clinically relevant. Such high doses may therefore have direct effects on mitochondrial electron transport, which may not be directly translatable to the effects expected at corresponding human doses. Further, we focused on drug effects at the neurotransmitter receptors level, but that is only one way drugs may indirectly alter mitochondrial activity. The observed considerable heterogeneity therefore needs to be considered indicating that not all effects can be explained at neurotransmitter receptors level. As an aside, the associations observed here are just "associations", they do not imply causality.

Conclusion

Summarizing the overall strength of mitochondrial changes caused by the seven drug categories indicates that antidepressants have the most heterogenous effects on both complex I and IV, which may be attributed to their broad receptor profiles including affinity to adrenergic (α), histaminergic

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(H1-4), muscarinic (M1-5), opioid (OP1-3), serotonergic (5-HT_{2A}, 5-HT_{2C}, 5-HT_{3A}), and sigma (σ1) receptors. Typical versus atypical antipsychotics show strong negative effects on complex I versus weaker or no positive effects on complex IV, most likely associated with differential affinity for dopaminergic (D2), and serotonergic (5-HT_{2A}) receptors. Stimulants also exhibit strong negative effects on complex I, potentially related to their inhibition of DAT, NET, and SERT transporters. Why stimulants and typical antipsychotics share a negative effect on complex I is hard to relate to the worsening of positive symptoms of psychosis by stimulants and the improvement by antipsychotics. In contrast, positive effects on complex I and/or IV are observed for anxiolytics, mood stabilizers, antidementia, and antiparkinsonian drugs, potentially associated with GABAergic (GABA-A), glutamatergic (AMPA, NMDA), and nicotinic (nACh) receptor effects. Further research is required, to better understand the connection between the actions of therapeutic agents and mitochondrial complexes. This may contribute to the development of mitochondrial targeted treatments in psychiatric and neurogenerative disorders.[169]

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Author contributions

L.H. collected the data, performed the analysis, and drafted the manuscript. B.BS. and J.J.M. provided helpful discussions and feedback to the manuscript. All authors agreed on the final version of the manuscript.

Data sharing statement

Aggregated data collected for the meta-analysis are made available in the supplementary materials (Datasets 1 and 2).

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Figures

Fig. 1. Forest plot: Drugs. Multivariate estimates of the effects (SMD, 95% CI, p-values) of antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia drugs and antiparkinsonian drugs on complex I and IV enzyme activities. Values lower than 0 indicate that treated animals had lower levels than controls, and vice versa for values greater than 0; the dashed vertical line at SMD = 0 indicates no effect. The size of the filled circles for each estimated SMD is proportional to the weight of the studies.

Fig. 2. Forest plot: Mechanism of action. Multivariate estimates of the effects (SMD, 95% CI, p-values) on complex I and IV enzyme activities of mechanisms of action of antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia drugs and antiparkinsonian drugs. Values lower than 0 indicate that animals treated had lower levels than controls, and vice versa for values greater than 0; the dashed vertical line at SMD = 0 indicates no effect. The size of the filled circles for each estimated SMD is proportional to the weight of the studies.

Antipsychotics (APs), antiepileptic drugs (AEGs), cholinesterase inhibitors (ChEIs), dopamine agonists (DAGs), dopamine reuptake inhibitors (DRIs), gamma-aminobutyric acid (GABA)A receptor positive allosteric modulators (PAMs), monoamine oxidase inhibitors (MAOIs), muscarinic M1 agonists (M1 AGs), N-methyl-D-aspartate receptor antagonists (NMDA ANTs), noradrenergic and specific serotonergic antidepressants (NaSSAs), norepinephrine-dopamine disinhibitors (NDDIs), norepinephrine–dopamine reuptake inhibitors (NDRIs), norepinephrine reuptake inhibitors (NRIs), reversible inhibitors of monoamine oxidase A (RIMAs), serotonin antagonist and reuptake inhibitors (SARIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake enhancers (SSREs), selective serotonin reuptake inhibitors (SSRIs).

Fig. 3. Forest Plot: Receptor affinity. Multivariate estimates of the effects (SMD, 95% CI, p-values) on complex I and IV enzyme activities by receptor affinity of antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia drugs and antiparkinsonian drugs. Values lower than 0 indicate that animals treated had lower levels than controls, and vice versa for values greater than 0; the dashed vertical line at SMD = 0 indicates no effect. The size of the filled circles for each estimated SMD is proportional to the weight of the studies. Type of receptor binding, i.e., agonism

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(AG) or antagonism (ANT), is indicated. See **Fig. S1, Dataset S2** for included drugs and affinity profiles.

Adrenergic (α,β), dopaminergic (D), GABAergic (GABA-A), glutaminergic (NMDA, AMPA), histaminergic (H), muscarinic (M), nicotinic (nACh), opioid (OP), serotonergic (5-HT), sigma (σ). DAT, NET and SERT correspond to the abilities of the drugs to inhibit the reuptake of dopamine, norepinephrine and serotonin, respectively.

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Tab. 1. Eligible studies. 68 studies were eligible for the meta-analyses covering 53 drugs. Mechanisms of actions are indicated [56]. Some studies reported more than one drug. The detailed data extracted from these studies are provided in **Dataset S1 & S2**.

Antipsychotics (APs), antiepileptic drugs (AEGs), cholinesterase inhibitors (ChEIs), dopamine agonists (DAGs), dopamine reuptake inhibitors (DRIs), gamma-aminobutyric acid (GABA)A receptor positive allosteric modulators (PAMs), monoamine oxidase inhibitors (MAOIs), muscarinic M1 agonists (M1 AGs), N-methyl-D-aspartate receptor antagonists (NMDA ANTs), noradrenergic and specific serotonergic antidepressants (NaSSAs), norepinephrine-dopamine disinhibitors (NDDIs), norepinephrine–dopamine reuptake inhibitors (NDRIs), norepinephrine reuptake inhibitors (NRIs), reversible inhibitors of monoamine oxidase A (RIMAs), serotonin antagonist and reuptake inhibitors (SARIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake enhancers (SSREs), selective serotonin reuptake inhibitors (SSRIs).

Antidepressants	**Complex**	**Mechanism**	**Author**
Agomelatine	I, IV	NDDI	Gupta 2014 [85], Kumar 2015 [86], Singh 2015 [170], de Mello 2015 [84]
Amitriptyline	I, IV	NRI	González-Pardo 2008 [69], Hroudová 2010 [16]
Bupropion	I, IV	NDRI	Ferreira 2012 [171]
Citalopram	I, IV	SSRI	Hroudová 2010 [16]
Desipramine	I, IV	NRI	Hroudová 2010 [16], Villa 2017 [64]
Escitalopram	I, IV	SSRI	Gonçalves 2012 [59]
Fluoxetine	I, IV	SSRI	Adzic 2013 [60], Padilla 2011 [62], Shumake 2010 [63], Villa 2017 [64]
Fluvoxamine	I, IV	SSRI	Ferreira 2014 [61]
Imipramine	I, IV	SNRI	Abelaira 2011 [172], Della 2012 [173], Hroudová 2010 [16], Ignácio 2015 [174], Kumar 2010 [68], Réus 2012 [148]
Ketamine	I, IV	NMDA ANT	Rezin 2009 [175], Rezin 2010 [94], Réus 2015 [93], Venâncio 2015 [95], de Oliveira 2011 [92]
Mirtazapine	I, IV	NaSSA	Hroudová 2010 [16]
Moclobemide	I, IV	RIMA	Hroudová 2010 [16]
Nortriptyline	I, IV	NRI	Scaini 2011 [66]
Paroxetine	I, IV	SSRI	Garabadu 2015 [65], Scaini 2011 [66]
Sertraline	I, IV	SSRI	Gaur 2010 [67], Kumar 2010 [68], Sharma 2016 [163]
Tianeptine	I, IV	SSRE	Della 2012 [173], Della 2013 [176], Hroudová 2010 [16]
Trazodone	I, IV	SARI	Kumar 2010 [68]
Venlafaxine	I, IV	SNRI	Hroudová 2010 [16], Kumar 2010 [68], Scaini 2011 [66], Sharma 2016 [163]
Antipsychotics	**Complex**	**Mechanism**	**Author**
Aripiprazole	I, IV	Atypical AP	Scaini 2013 [177], Streck 2007 [104]
Chlorpromazine	I, IV	Typical AP	Balijepalli 1999 [98], Burkhardt 1993 [101]
Clozapine	I, IV	Atypical AP	Balijepalli 1999 [98], Balijepalli 2001 [99], Burkhardt 1993 [101], Prince 1997 [102], Prince 1998 [103], Przedborski 1995 [178], Scaini 2013 [177], Streck 2007 [104]
Fluphenazine	I, IV	Typical AP	Balijepalli 1999 [98], Prince 1997 [102], Prince 1998 [103]
Haloperidol	I, IV	Typical AP	Balijepalli 1999 [98], Balijepalli 2001 [99], Barrientos 1998 [100], Burkhardt 1993 [101], Prince 1997 [102], Prince 1998 [103], Streck 2007 [104]
Molindone	I	Typical AP	Przedborski 1995 [178]
Olanzapine	I, IV	Atypical AP	Hroudová 2010 [16], Scaini 2013 [177], Streck 2007 [104]
Quetiapine	I, IV	Atypical AP	Ignácio 2015 [174]
Risperidone	I, IV	Atypical AP	Balijepalli 1999 [98], Balijepalli 2001 [99], Garabadu 2015 [65]

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Thiothixene	I, IV	Typical AP	Burkhardt 1993 [101]
Anxiolytics	**Complex**	**Mechanism**	**Author**
Clonazepam	I, IV	GABA-A PAM	Mohamed 2013 [179]
Diazepam	I, IV	GABA-A PAM	Kumar 2014 [132], van der Kooij 2018 [180]
Mood stabilizers	**Complex**	**Mechanism**	**Author**
Gabapentin	I, IV	AEG	Kumar 2012 [131], Kumar 2014 [132]
Lamotrigine	I, IV	AEG	Abelaira 2011 [172], Kumar 2012 [131]
Lithium	I, IV	Lithium	Bachmann 2009 [119], Feier 2013 [120], Hroudová 2010 [16], Kim 2016 [121], Lambert 1999 [122], Tan 2012 [123], Valvassori 2010 [124]
Topiramate	I, IV	AEG	Kudin 2004 [181]
Valproic acid	I, IV	AEG	Bachmann 2009 [119], Feier 2013 [120], Hroudová 2010 [16], Mishra 2014 [140], Valvassori 2010 [124]
Stimulants	**Complex**	**Mechanism**	**Author**
Amphetamine	I	DRI	Tan 2012 [123]
Mazindol	I, IV	DRI	Gonçalves 2014 [138]
Methamphetamine	I, IV	DRI	Brown 2005 [135], Killinger 2014 [139], Thrash 2010 [141], Thrash-Williams 2013 [142], Thrash-Williams 2016 [143]
Methylphenidate	I, IV	DRI	Fagundes 2007 [136], Fagundes 2010 [137]
Antidementia	**Complex**	**Mechanism**	**Author**
7-MEOTA	I, IV	Unknown	Singh 2017 [149]
Donepezil	I, IV	ChEI	Singh 2015 [170], Singh 2017 [149]
Galantamine	I, IV	ChEI	Singh 2015b [87], Singh 2017 [149]
Latrepirdine	I, IV	Unknown	Singh 2017 [149]
Memantine	I, IV	NMDA ANT	Kumar 2016 [147], Réus 2012 [148], Singh 2017 [149]
Piracetam	I, IV	Unknown	Singh 2017 [149]
Rivastigmine	I, IV	ChEI	Kumar 2009 [182], Singh 2017 [149]
Antiparkinsonian	**Complex**	**Mechanism**	**Author**
Amantadine	I	Unknown	Thrash-Williams 2013 [142]
Bromocriptine	I	DAG	Przedborski 1995 [178]
Levodopa	I, IV	DAG	Abdin 2008 [160], Calabrese 2007 [161], Dixit 2013 [159], Przedborski 1993 [162], Sharma 2016 [163]
Minocycline	I	Unknown	Dixit 2013 [159]
Pergolide	I	DAG	Przedborski 1995 [178]
Selegiline	I, IV	MAOI	Czerniczyniec 2006 [164], Przedborski 1995 [178], Saravanan 2006 [183]
Trihexyphenidyl	I	M1 AG	Przedborski 1995 [178]

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Tab. 2. Heterogeneity and Inconsistency. Significant Q statistics indicate the existence of heterogeneity. A I^2 value of 0% indicates no observed inconsistency, whereas larger values shows increasing inconsistency. **Egger's regression test for publication bias.** The existence of potential publication bias is indicated by p-values < 0·05. df = degrees of freedom.

Heterogeneity and Inconsistency				
		Q	**p-value**	**I^2 (%)**
Complex I	**Antidepressants**	682·00	0·000	86%
	Antipsychotics	533·87	0·000	87%
	Anxiolytics	34·99	0·000	89%
	Mood stabilizers	131·09	0·000	85%
	Stimulants	45·93	0·434	11%
	Antidementia drugs	122·33	0·000	71%
	Antiparkinsonian drugs	83·39	0·000	84%
Complex IV	**Antidepressants**	707·35	0·000	71%
	Antipsychotics	661·47	0·000	76%
	Anxiolytics	4·57	0·102	87%
	Mood stabilizers	339·63	0·000	80%
	Stimulants	111·71	0·000	53%
	Antidementia drugs	57·39	0·000	63%
	Antiparkinsonian drugs	5·58	0·589	34%
Egger's regression				
		z-value	**df**	**p-value**
Complex I	**Antidepressants**	1·74	22	0·095
	Antipsychotics	-1·36	8	0·211
	Anxiolytics	0·49	2	0·671
	Mood stabilizers	1·54	8	0·161
	Stimulants	-0·13	7	0·902
	Antidementia drugs	-1·16	4	0·311
	Antiparkinsonian drugs	1·23	7	0·258
Complex IV	**Antidepressants**	0·44	24	0·665
	Antipsychotics	0·23	7	0·822
	Anxiolytics	3·73	1	0·167
	Mood stabilizers	1·10	8	0·302
	Stimulants	0·64	4	0·558
	Antidementia drugs	-0·07	3	0·949
	Antiparkinsonian drugs	0·97	1	0·511

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Figure1

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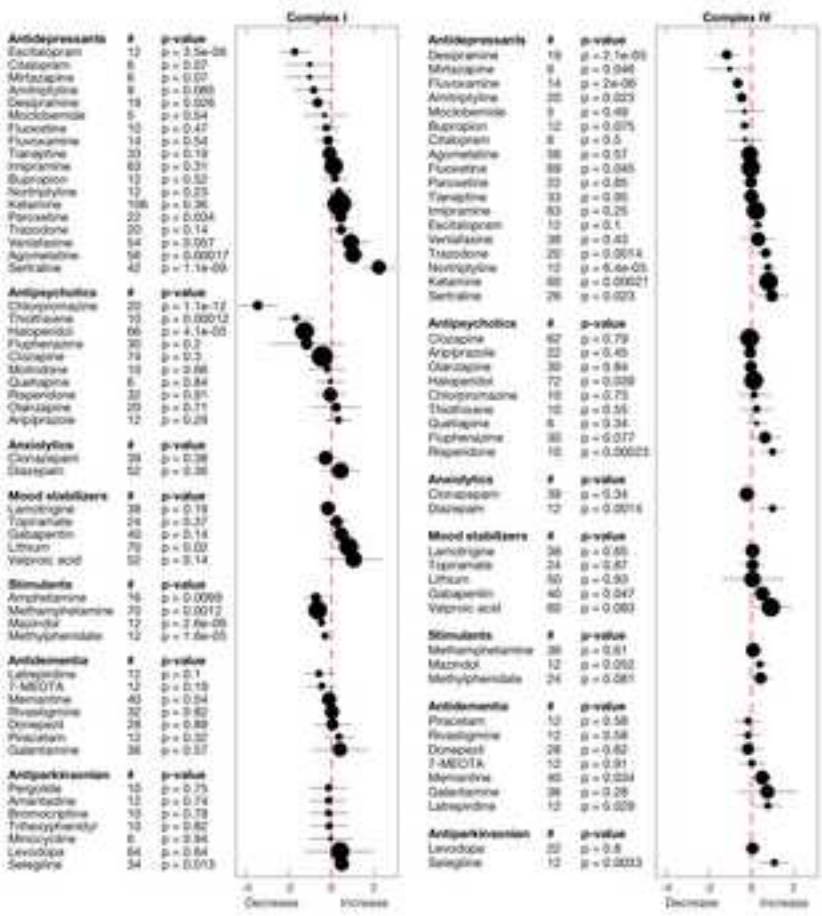

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Figure2

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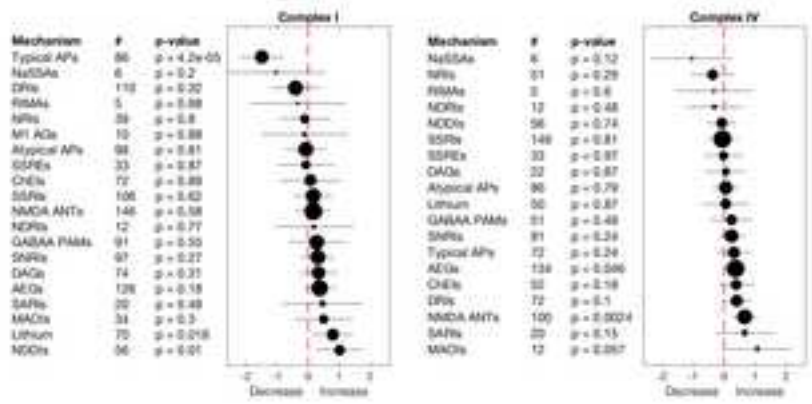

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Figure3

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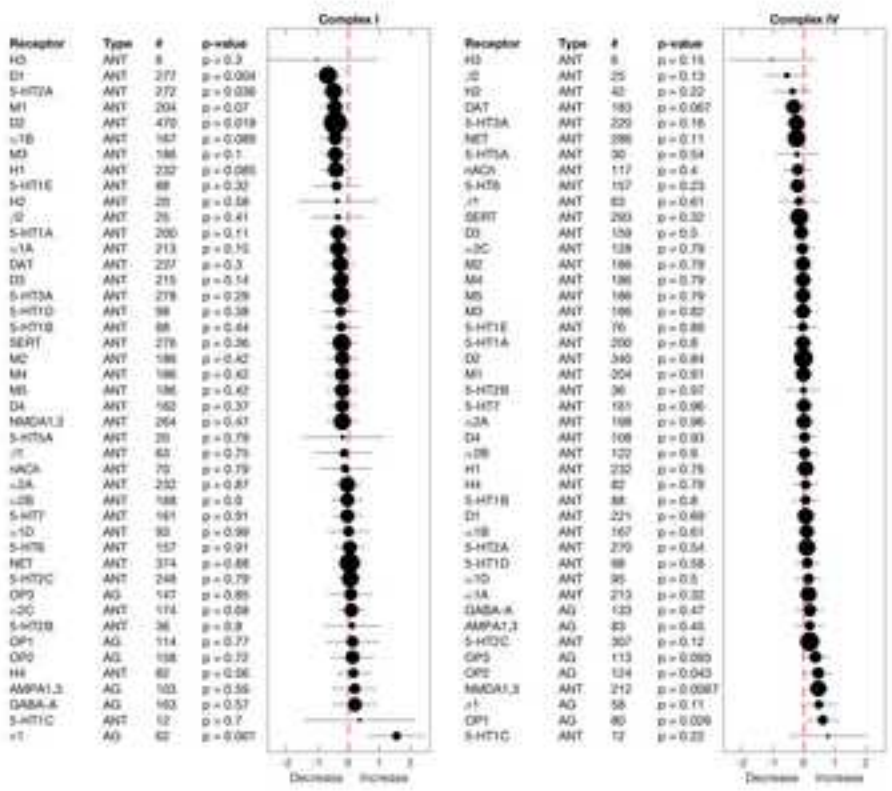

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